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| 09/448,042 | 11/23/1999 | STANLEY N. LAPIDUS | EXT-023 | 4602 |

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TESTA, HURWITZ & THIBEAULT, LLP
HIGH STREET TOWER
125 HIGH STREET
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| ARTHUR, LISA BENNETT | |

| ART UNIT | PAPER NUMBER |
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| 1634 | 9 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/448,042 | Applicant(s) LAPIDUS ET AL. | |
|---|---|---|---|
| | Examiner Lisa B. Arthur | Art Unit 1655 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4,10-12,15,18-20 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,4,10-12,15, 18-20,24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the paper filed January 23, 2002. Currently, claims 1,4,10-12,15, 18-20, 24 and newly added claims 25-27 are pending. All of the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance for the reasons which follow. Any rejections which have not been reiterated have been obviated by the amendments made to the claims. This rejection contains new grounds of rejection which have been necessitated by the amendment of the claims to recite that the primer is exposed to the biological sample such as stool, blood or urine rather than to the nucleic acid obtained from a biological sample.

## NEW GROUNDS OF REJECTION

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1,4,10-12, 15,18,20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of JP 09187277 (abstract, July 22, 1997).

Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer covalently labeled with a fluorescent dye, performing primer extension in presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to

produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2). Kwok et al. Teaches the limitation of claim 4 by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (see example 5, column 21, line 40 through column 23). Kwok et al. Teach the limitation of claim 10 by teaching the use of 6-carboxy-X rhodamine, N,N,N,N-tetramethyl-6-carboxyrhodamine, 6-carboxy-X-rhodomine, and fluorescein (Table 1) and teaches that any number of fluorophore combination can be use in their method (column 7, lines 52-60). Kwok et al. Teach the use of their method to detect a nucleic acid mutation (see examples 4 and 5) (limitation of claim 18) and to detect a single nucleotide polymorphism (see example 2) (limitation of claim 20).

While Kwoh et al. does teach that their method can be performed on a nucleic acid sample obtained from virtually any source (column 9, lines 35-44), Kwok et al does not specifically exposing the primer to a stool, urine or blood sample. However, JP09187277 discloses a method for performing nucleic acid extension and PCR amplification directly on a sample of whole blood.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok et al. to a patient blood sample of JP09187277 in order to make the claimed invention as a whole because JP09187277 taught that a nucleic acid PCR method could be performed on nucleic acid from whole blood without isolation of the nucleic acid from the whole blood

sample such that the ordinary artisan would have been motivated to analyze the blood sample using the method of Kowh et al which provided more sensitive and specific results. The ordinary artisan would have been motivated to have modified the method of Kwoh et al. to use the whole blood sample of JP 09187277 in order to have achieved the expected result of reduce the number of method steps required to obtain the nucleic acid for the Kwoh et al. method with the expectation that the Kwoh et al. would have been successful on this sample since JP09187277 showed that nucleic acid could be detectably amplified by exposure of a primer to the whole blood sample.

2. Claims 1,4,10-12, 15,18,20, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of Gillespie

Kwok et al. teaches a method for determining the presence of a target nucleotide by adding to a DNA sample a primer convalently labeled with a fluorescent dye, performing primer extension in presence of a dideoxynucleotide covalently labeled with a fluorescent dye capable of being activated through fluorescent energy transfer to produce a detectable fluorescent signal when the dideoxynucleotide is incorporated into the extension product, determining the presence of the fluorescent signal and thereby determining the presence of the target nucleotide (see abstract, Figure 1, column 3; lines 21-33 and examples 1-2). Kwok et al. Teaches the limitation of claim 4 by teaching that the extension reaction could be performed in the presence of at least two different dideoxynucleotides (see example 5, column 21, line 40 through column 23). Kwok et al. Teach the limitation of claim 10 by teaching the use of 6-carboxy-X

rhodamine, N,N,N,N-tetramethyl-6-carboxyrhodamine, 6-carboxy-X-rhodomine, and fluorescein (Table 1) and teaches that any number of fluorophore combination can be use in their method (column 7, lines 52-60). Kwok et al. Teach the use of their method to detect a nucleic acid mutation (see examples 4 and 5) (limitation of claim 18) and to detect a single nucleotide polymorphism (see example 2) (limitation of claim 20).

While Kwoh et al. does teach that their method can be performed on a nucleic acid sample obtained from virtually any source (column 9, lines 35-44), Kwok et al does not specifically exposing the primer to a stool, urine or blood sample. However, Gillespie discloses a method for a nucleic acid hybridization detection method on a sample of whole blood (column 49, 51-52) or stool (column 50) without an additional nucleic acid isolation step. Gillespie also taught that their method applies to many different biological samples including blood, lymph, urine, saliva, pieces of tissue (column 7, lines 62-67).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok et al. to a patient blood or stool sample of Gillespie in order to make the claimed invention as a whole because Gillespie taught that a nucleic acid hybridization method could be performed on nucleic acid from whole blood or stool without isolation of the nucleic acid from the whole blood or stool sample such that the ordinary artisan would have been motivated to analyze the blood sample using the method of Kowh et al which provided more sensitive and specific results. The ordinary artisan would have been motivated to have modified the method of Kwoh et al. to use the whole blood or stool sample of

Gillespie in order to have achieved the expected result of reduce the number of method steps required to obtain the nucleic acid for the Kwoh et al. method with the expectation that the Kwoh et al. would have been successful on this sample since Gillespie showed that nucleic acid could be detectably hybridized and detected by exposure of a labeled probe to the whole blood or stool sample.

3. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of JP09187277 are applied to claims 1,4,10-12, 15,18,20 and 25 and further in view of Lu et al. (abstract)

Kwoh et al. combined with the teachings of JP09187277 does not specifically teach applying the method to the detection of mutations in the p53, apc, or ras genes. However, Lu et al. teach that the p53, apc and ras genes are all known to be oncogenes involved in a number of different cancers.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the nucleotide detection method of Kwok et al. in view of JP09187277 to the detection of mutations in p53, apc and ras because Lu et al. taught that these genes were known to be involved in cancer and that the detection of mutations was important for the diagnosis and prognosis of cancer.

4. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kwok et al. in view of JP09187277 are applied to claims 1,4,10-12, 15,18,20 and 25 above and further in view of O'dell et al. (Clin. Chem. (1998) 44(1): 183-185.

Kwok et al. combined with the teachings of JP09187277 does not teach using a sample from a pooled patient population.

However, O'dell et al. taught a method of analyzing a target nucleic acid for the presence of mutations associated with disease by screening pooled DNA samples.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the method of Kwok et al. in view of JP09187277 to the screening of pooled DNA samples as taught by O'dell et al. because O'dell et al. taught that screening pooled DNA samples allowed the efficient and cost-effective processing of a large number of specimens.

5. No claims are allowable over the prior art.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Applicant should note that the examiner handling this application has now been changed. Any inquiry concerning this communication or earlier communications from the examiner should be now directed to Lisa B. Arthur whose telephone number is 308-3988. The examiner can normally be reached on Monday-Wednesday from 7:00 am to 2:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

April 22, 2002